Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization.

AUTHOR(S):

Oishi, Akio; Yamashiro, Kenji; Tsujikawa, Akitaka; Ooto, Sotaro; Tamura, Hiroshi; Nakata, Isao; Miyake, Masahiro; Yoshimura, Nagahisa

CITATION:

Oishi, Akio ...[et al]. Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization.. Graefe's archive for clinical and experimental ophthalmology 2013, 251(1): 1-7

ISSUE DATE:

2013-01

URL:

http://hdl.handle.net/2433/169724

21, Jan, 2012

Professor Joussen,
Professor Wong,
Editor in Chief
Graefe's Archives of Ophthalmology

Dear Sir:

I, along with my coauthors, would like to ask you to consider the attached manuscript entitled "**Long-term effect of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization**" for publication in the **Graefe's Archives of Ophthalmology** as a full-length article.

Therapeutic tools targeting vascular endothelial growth factor (VEGF) are becoming a standard for myopic choroidal neovascularization (mCNV). In this hospital-based, retrospective study involving 22 patients with treatment-naïve mCNV, we found that the anti-VEGF monoclonal antibody bevacizumab was efficient at improving visual acuity in the four year period, albeit induction of chorioretinal atrophy was observed in many cases and warranted further investigation.

We believe that the findings of this study are relevant to the scope of your journal and will be of interest to its readership.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards. All the authors have approved the manuscript and agree with submission to your esteemed journal. There are no conflicts of interest to declare. I, the corresponding author, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication.

I look forward to hearing from you at your earliest convenience.

Sincerely,
Akio Oishi
Department of Ophthalmology
Kyoto University Graduate School of Medicine
Sakyo-ku, Kyoto 606-8507, Japan
Tel: +81-75-751-3250
Fax: +81-75-752-0933
E-mail: aquio@kuhp.kyoto-u.ac.jp

Reviewer comments:

Reviewer #1: Dear Authors,

The MS entitled Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization is interesting because it provides long term outcoms of myopic CNV after treatment with anti-VEGF.

However, considering this study, it could be interesting to mention the characteristics of CNV (size) at the beginning of the study, to show if initial CNV size is partly correlated to the development of CRA.

> Thank you for your comment. Actually, we evaluated the effect of initial CNV size with logistic regression analysis (page 4 paragraph 2) and found non-significant contribution. Spearman rank correlation was additionally performed and it showed the correlation between CNV size and visual improvement. The analysis and the result were added in method and result sections. (page 4 paragraph 3, page 6 paragraph 1)

Reviewer #2: A well written manuscript.

> Thank you for your kind comment.

Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization

Akio Oishi, Kenji Yamashiro, Akitaka Tsujikawa, Sotaro Ooto, Hiroshi Tamura, Isao Nakata, Masahiro Miyake, Nagahisa Yoshimura

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Corresponding author:

Akio Oishi, Department of Ophthalmology, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto 606-8507, Japan

Tel: +81-75-751-3250

Fax: +81-75-752-0933

E-mail: aquio@kuhp.kyoto-u.ac.jp

There is no financial support or propriety interest concerning the article.

Abstract

Purpose: To investigate the long-term visual prognosis and progression of chorioretinal atrophy in patients with myopic choroidal neovascularization (mCNV) treated with intravitreal injections of Bevacizumab.

Methods: Hospital-based, retrospective cross sectional study. In total, 22 patients (22 eyes) with treatment-naïve mCNV who underwent intravitreal injection of bevacizumab and were followed up for more than 48 months were investigated. Visual acuity and fundus photographs before and 1, 2, 3, and 4 years after initial treatment in the clinics were compared and judged if chorioretinal atrophy (CRA) developed/enlarged or remained unchanged. The influence of clinical characteristics including age, sex, axial length, baseline visual acuity, CNV area, CNV location, and number of injections were investigated with logistic regression analysis.

Results: Mean logarithm of the minimum angle of resolution (logMAR) improved from 0.76 to 0.52 ($P < .01$), 0.48 ($P < .01$), and 0.54 ($P < .05$) after 1, 2, and 3 years, respectively. The effect slightly declined to marginally non-significant levels after 4 years (logMAR, 0.59; $P = .07$). CRA developed or enlarged in 9 cases (41%) in 1 year, reaching 16 cases (73%) at the final visit. Those without CRA enlargement achieved better visual improvement. None of the aforementioned patient characteristics significantly affected CRA.

Conclusions: Anti-VEGF therapy for mCNV is effective for vision improvement in the long term. On the other hand, development or enlargement of CRA frequently occurred and affected visual improvement. Strategies to manage atrophy should be the next step in achieving better visual outcome upon mCNV treatment.

Introduction

Pathologic myopia is one of the major causes of visual impairment worldwide. The disease, marked by elongation of axial length and changes in the fundus of the eye, may cause complications such as posterior staphyloma, chorioretinal atrophy (CRA), or choroidal neovascularization (CNV). Considering that myopia is more prevalent in younger populations,[1, 2] the impact on social health will be more profound in the near future.

Myopic CNV (mCNV) is reported to occur in up to 10% of myopic patients,[3] with a prevalence of up to 40% in highly myopic patients.[4] Since long-term visual prognosis is poor in the absence of treatment,[5, 6] a wide range of therapeutic alternatives, including photocoagulation, macular translocation, surgical CNV removal, administration of triamcinolone acetonide, and photodynamic therapy (PDT), have been explored.[7] Although PDT can stabilize the disease activity, formation of subretinal fibrosis[8] or CRA, a cause of the poor natural course of mCNV,[6, 9] frequently occurs after the treatment,[10] and may affect visual function significantly in the long term. In fact, the most reliable trial (Verteporfin In Photodynamic Therapy: VIP study) failed to show significant improvement in vision 2 years after the treatment.[11]

After the PDT era, anti-vascular endothelial growth factor (VEGF) therapy was developed and proved to be effective against mCNV.[12-24] Although the treatment regimens were not equivalent in these studies, intravitreal anti-VEGF therapy seems to promote the regression of CNV more effectively and decrease the frequency of CRA, compared to PDT.[25-28] However, even with anti-VEGF therapy, CRA still develops[17, 18, 24, 25] and may affect the long-term visual prognosis. [24] In fact, vision improvement became non-significant in some of these studies by the end of 2 years of follow-up.[17, 29-31] Although a recent report showed favorable effects after 3 years of follow-up,[32] some of the studied subjects had previously been treated with PDT. Thus, long-term prognosis of anti-VEGF therapy, especially for treatment-naïve mCNV, is still unclear.

In the present study, we investigated long-term visual prognosis of treatment-naïve mCNV patients who underwent anti-VEGF therapy. We also investigated how often CRA progression occurs in these patients, and explored the difference between those with and without CRA enlargement.

Methods

All procedures conformed to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board at Kyoto University Graduate School of Medicine. Written informed consent was obtained from each patient.

We retrospectively reviewed the clinical records of mCNV patients. Inclusion criteria were as follows: 1) presence of subfoveal or juxtafoveal CNV, 2) refractive error greater or equal to -6.0 diopters or axial length greater or equal to 26.5 mm, 3) underwent intravitreal injection of 1.25 mg bevacizumab at Kyoto University Hospital, and 4) no previous ocular surgery other than phacoemulsification and aspiration for cataract. When both eyes of one patient met the inclusion criteria, only the right eye was included. Exclusion criteria were: 1) any treatment for mCNV other than anti-VEGF therapy prior to or during the observation period, 2) a follow-up period of less than 48 months, and 3) intraocular surgery or development of other ocular diseases during the follow-up.

Initial and follow-up fluorescein angiography (FA) was performed with a confocal scanning laser ophthalmoscope (HRA2; Heidelberg Engineering, Heidelberg, Germany), and 45-degree fundus photographs are taken with a fundus camera (TRC NW6S; TOPCON, Tokyo, Japan). Injections of 1.25 mg bevacizumab were performed under sterile conditions, and prophylactic topical antibiotics were applied from a few days before to 1 week after the injection. Follow-up intervals were 1, 3, 6, 12, 18, 24, 30, 36, and 48 months. Additional follow-up was planned for each patient at the clinician's discretion. Visual acuity, funduscopic examination, and optical coherence tomography (OCT) examination were performed at each visit. FA was performed when subjective symptoms worsens but OCT does not show obvious exudative changes. After

the initial treatment, additional treatment was applied as needed. The need for re-treatment was determined according to objective/subjective decline of vision, exudative changes in OCT images, and/or dye leakage in FA. Same dose of Bevacizumab had been injected for re-treatment until December, 2008 when we encountered the outbreak of aseptic endophthalmitis. [33] Thereafter, 0.3 mg of Pegaptanib had been used for five months. Then after use of Ranibizumab was officially approved in May 2009, 0.5 mg of Ranibizumab was applied for the recurrences.

Development or enlargement of CRA was judged with photographs taken each year by 2 of the authors (AO and KY) who were blinded to the other characteristics of the patient. The judgment was based on changes in patchy atrophy; color changes in tessellation or diffuse atrophy without patchy atrophy were not considered as CRA progression (Figure 1). CRAs, which were not adjacent to original CNV location, were not counted. When the 2 authors disagreed, a third author (AT) was asked to arbitrate. The CNV area was manually measured in early-phase FA images with measuring tools, which were coupled to the HRA2. Location of CNV was judged from FA; those involving the center of the foveal avascular area on FA were judged as subfoveal. When it was difficult to judge only from FA images, OCT images were used to confirm whether CNV membranes lied beneath the fovea.

Formatted: Underline

Statistical analyses were conducted using IBM SPSS Statistics Desktop (version 19.0; IBM Japan, Tokyo, Japan). Descriptive analyses were recorded as means ± standard deviation unless otherwise specified. The BCVA was measured based on a Landolt C chart and then converted to logarithm of the minimal angle of resolution (logMAR) equivalents. Differences in VA from baseline were analyzed using repeated measures ANOVA with post-hoc Tukey's test. Logistic regression analysis of the clinical variables was performed with development/enlargement of CRA as the dependent variable. Independent variables were chosen based on forward stepwise regression. Correlations between the variables were also evaluated with Spearman rank correlation. Differences in age, axial length, BCVA, and number of injections between those

with and without CRA progression were evaluated with Mann–Whitney *U*-test. Chi-square test was applied to assess the difference in sex or CNV location (subfovea/juxtafovea) between those with and without CRA progression.

Results

Forty eyes of 40 patients met the inclusion criteria. Two patients had bilateral involvement but only their right eyes were included. We excluded one patient who developed aseptic endophthalmitis, one who developed central retinal vein occlusion, 2 who underwent vitrectomy for retinoschisis, and 4 who underwent additional PDT. Ten patients dropped out before the end of the 48 months of follow-up. Finally, 22 eyes of 22 patients were eligible for the study. Among them, 7 were men and 15 were women. The mean age of the participants was 64.1 ± 9.6 years (range, 47 to 81 years), and axial length was 28.9 ± 1.6 mm (range, 26.28 to 32.63 mm). The refractive error of phakic patients was -11.9 ± 3.7 diopter (range, -7 to -21). Mean number of injections was 2.1 ± 1.9 (range, 1 to 7) including 41 times of Bevacizumab and six times of Ranibizumab injections.

Development or enlargement of CRA was noted in 9 eyes (40.9%) in 1st year, 14 eyes (63.6%) in 2nd years, and 16 eyes (72.7%) in 3rd and 4th years; those without CRA progression after 3 years did not show remarkable change in the fourth year. Logistic regression analysis showed non-significant effect of age (P = .08) and location of CNV for CRA progression at 1 year (P = .07). After 2 years, none of the parameters showed significant effect. Table 1 shows characteristics of those with and without CRA progression at 4 years after the treatment. Visual improvement was better in those without CRA progression than those with CRA progression. Those without CRA progression tended to include juxtafoveal CNV more frequently but the difference was not significant (P = .21). Representative cases are shown in Figures 1–5. Some patients developed CRA early after the treatment (Figure 1), whereas others developed CRA after 1 or 2 years (Figure 2). The minority of patients was free of CRA

progression during the course of the 48-month follow-up (Figure 3).

Visual acuity improved from baseline but slightly declined thereafter. The difference from baseline was significant until 3 years and was marginally insignificant at 4 years after the treatment (Figure 4). Among the baseline CNV characteristics, CNV size measured with FA image was associated with visual improvement (r=.434, P=.04); larger CNV resulted in poor visual improvement.

Discussion

We investigated long-term visual outcome and progression of CRA in treatment-naïve mCNV patients who underwent anti-VEGF therapy. The study showed significant improvement of vision over the 3 years of follow-up, despite that the *P* value was barely non-significant in the fourth year, and confirmed the beneficial effect of anti-VEGF therapy for mCNV. At the same time, the study showed that most patients finally experience the progression of CRA irrespective of baseline characteristics, and that CRA compromises the vision-improving effect.

Anti-VEGF therapy is becoming a standard treatment for mCNV although its application is not yet officially approved in many countries. The present study confirmed the long-term effect of the therapy. Considering that the effect of PDT is limited to maintain vision,[10,][34] anti-VEGF therapy should be the first choice until a novel method is proven to be more effective.

On the other hand, the present study raised some concerns regarding longer-term prognosis: the progression of CRA. Anti-VEGF therapy is considered to be superior to PDT partly because it induces CRA less frequently. However, the present result showed that the assumption is not necessarily applicable in the long term. In fact, CRA developed or enlarged in as many as 80% of the patients. Even considering that only 3/10 dropout patients showed CRA progression at their final visit, the percentage of patients with CRA progression should be at least $[(16 + 3)/(22 + 10)] \times 100 = 59.4\%$. This figure is comparable to the 70% in PDT-treated eyes after 4 years,[10] or the 77.8%

(35/45 eyes) in eyes after the natural course of 5 years[35] but not to the 95.1% reported for the 80 months result.[36] Hence, CRA progression is often an inevitable consequence in the long-term follow-up of mCNV cases, probably due to natural history but to anti-VEGF therapy. Considering that those with CRA progression showed less visual improvement, the control of CRA should be the next step to be investigated.

Older age has been associated with development of CRA[36] or poor visual outcome.[37],[38] However, the present study did not show significant contribution of age for the development of CRA. One explanation could be the existence of a critical age. Most of the previous studies investigated age-dependent differences by comparing aged and younger patients of 40 to 60 years of age. The population in the present study consisted of relatively older subjects; the average and median age of the participants in the present study was 64.1 and 64 years, respectively. A small percentage of young patients could explain the non-significant effect of age.

The location of CNV is of clinical interest. Several groups, including ours, showed that patients with juxtafoveal CNV have better prognosis than subfoveal CNV during the natural course of the disease[35] or after anti-VEGF therapy.[18, 39] Moreover, subfoveal CNV induces larger CRA after PDT than do juxtafoveal or extrafoveal CNV[10] or induce CRA more frequently after intravitreal injection of Bevacizumab.[24] In the present study, subfoveal CNV tended to cause CRA progression more frequently at 1 year after the initial treatment, although this was not statistically significant. Furthermore, 4 out of 6 patients who were free of CRA for 4 years had juxtafoveal CNV. The statistical non-significance may be partly due to the small sample size and the difficulty in treating recurrent cases: one case with juxtafoveal CNV recurred with subfoveal CNV and developed CRA thereafter. Although the underlying mechanism is not clear, e.g., could subfoveal CNV be a mere result of larger CNV size?, whether the location of CNV can be a practical prognostic parameter of CRA progression should be further investigated.

There still is a debate about which protocol is the most effective. Some

authors used 3 monthly injections at the loading phase, whereas others adopted a single injection followed by additional as-needed injections. The dose of the drug also varies among reports, with 1, 1.25, and 2.5 mg of bevacizumab having been reported to be effective. Although we cannot draw any conclusion from the non-comparative study, we prefer the single injection and as-needed regimen due to lower risk and smaller cost, considering the relatively young age, healthier RPE, and slower progression of mCNV[40] compared to age-related macular degeneration. Randomized or meta-analysis study should be conducted to address the issue.

There are several limitations to the present study, including its retrospective design, uncontrolled examination interval, small sample size, and lack of a control group. In addition, there have existed a selection bias, e.g., patients with persistent or recurrent CNV would more likely present to the hospital for a longer period or, conversely, patients with severe phenotypes might have undergone additional PDT and be excluded from the study. In addition, we did not investigate OCT images in detail because the resolution of the devices used when the patients underwent initial treatment was limited. Further evaluation of pretreatment OCT image including retinal layer thickness or choroidal thickness would be interesting. These points should be noted when interpreting the results.

In conclusion, we showed that anti-VEGF therapy had satisfactory vision-improving effect for a 4-year period but the treatment was not free of inducing CRA. To achieve better results, the causes and management of CRA should be further investigated.

References

1. Mutti DO, Zadnik K (2000) Age-related decreases in the prevalence of myopia: longitudinal change or cohort effect? Invest Ophthalmol Vis Sci 41: 2103-2107
2. Lee KE, Klein BE, Klein R, Wong TY (2002) Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. Invest Ophthalmol Vis Sci 43: 2566-2571
3. Curtin BJ (1963) The pathogenesis of congenital myopia. A study of 66 cases. Arch Ophthalmol 6: 166-173
4. Hotchkiss ML, Fine SL (1981) Pathologic myopia and choroidal neovascularization. Am J Ophthalmol 91: 177-183
5. Tabandeh H, Flynn HWJ, Scott IU, Lewis ML, Rosenfeld PJ, Rodriguez F, Rodriguez A, Singerman LJ, Schiffman J (1999) Visual acuity outcomes of patients 50 years of age and older with high myopia and untreated choroidal neovascularization. Ophthalmology 106: 2063-2067
6. Yoshida T, Ohno-Matsui K, Yasuzumi K, Kojima A, Shimada N, Futagami S, Tokoro T, Mochizuki M (2003) Myopic choroidal neovascularization: a 10-year follow-up. Ophthalmology 110: 1297-1305
7. Chan WM, Ohji M, Lai TY, Liu DT, Tano Y, Lam DS (2005) Choroidal neovascularisation in pathological myopia: an update in management. Br J Ophthalmol 89: 1522-1528
8. Ruiz-Moreno JM, Montero JA (2003) Subretinal fibrosis after photodynamic therapy in subfoveal choroidal neovascularisation in highly myopic eyes. Br J Ophthalmol 87: 856-859
9. Ohno-Matsui K, Yoshida T (2004) Myopic choroidal neovascularization: natural course and treatment. Curr Opin Ophthalmol 15: 197-202
10. Hayashi K, Ohno-Matsui K, Shimada N, Moriyama M, Hayashi W, Wang J, Yoshida T, Tokoro T, Mochizuki M (2011) Long-term results of photodynamic therapy for choroidal neovascularization in Japanese patients with pathologic myopia. Am J Ophthalmol 151: 137-147
11. Blinder KJ, Blumenkranz MS, Bressler NM, Bressler SB, Donato G, Lewis

H, Lim JI, Menchini U, Miller JW, Mones JM, Potter MJ, Pournaras C, Reaves A, Rosenfeld P, Schachat AP, Schmidt-Erfurth U, Sickenberg M, Singerman LJ, Slakter JS, Strong HA, Virgili G, Williams GA (2003) Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial--VIP report no. 3. Ophthalmology 110: 667-673

12. Gharbiya M, Allievi F, Mazzeo L, Gabrieli CB (2009) Intravitreal bevacizumab treatment for choroidal neovascularization in pathologic myopia: 12-month results. Am J Ophthalmol 147: 84-93
13. Konstantinidis L, Mantel I, Zografos L, Ambresin A (2009) Intravitreal ranibizumab as primary treatment for neovascular membrane associated with idiopathic juxtafoveal retinal telangiectasia. Graefes Arch Clin Exp Ophthalmol 247: 1567-1569
14. Silva RM, Ruiz-Moreno JM, Rosa P, Carneiro A, Nascimento J, Rito LF, Cachulo ML, Carvalheira F, Murta JN (2010) Intravitreal Ranibizumab for Myopic Choroidal Neovascularization 12-Month Results. Retina 30: 407-412
15. Mones JM, Amselem L, Serrano A, Garcia M, Hijano M (2009) Intravitreal ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results. Eye (Lond) 23: 1275-1280
16. Lai TY, Chan WM, Liu DT, Lam DS (2009) Intravitreal ranibizumab for the primary treatment of choroidal neovascularization secondary to pathologic myopia. Retina 29: 750-756
17. Lalloum F, Souied EH, Bastuji-Garin S, Puche N, Querques G, Glacet-Bernard A, Coscas G, Soubrane G, Leveziel N (2010) Intravitreal ranibizumab for choroidal neovascularization complicating pathologic myopia. Retina 30: 399-406
18. Calvo-Gonzalez C, Reche-Frutos J, Donate J, Fernandez-Perez C, Garcia-Feijoo J (2011) Intravitreal ranibizumab for myopic choroidal neovascularization: factors predictive of visual outcome and need for retreatment. Am J Ophthalmol 151: 529-534
19. Falcao-Reis FM, Carneiro AM, Silva RM, Veludo MJ, Barbosa A,

Ruiz-Moreno JM, Falcao MS, Brandao EM (2011) Ranibizumab treatment for choroidal neovascularization from causes other than age-related macular degeneration and pathological myopia. Ophthalmologica 225: 81-88

20. Iacono P, Parodi MB, Papayannis A, Kontadakis S, Sheth S, Bandello F (2011) Intravitreal bevacizumab therapy on an as-per-needed basis in subfoveal choroidal neovascularization secondary to pathological myopia: 2-year outcomes of a prospective case series. Retina 31: 1841-1847
21. Ruiz-Moreno JM, Montero JA, Arias L, Araiz J, Gomez-Ulla F, Silva R, Pinero DP (2010) Twelve-month outcome after one intravitreal injection of bevacizumab to treat myopic choroidal neovascularization. Retina 30: 1609-1615
22. Chen CH, Wu PC, Chen YJ, Liu YC, Kuo HK (2011) Intravitreal injection of 2.5 mg bevacizumab for treatment of myopic choroidal neovascularization in treatment-naive cases: a 2-year follow-up. J Ocul Pharmacol Ther 27: 395-400
23. Vadala M, Pece A, Cipolla S, Monteleone C, Fasolino G, Casuccio A, Cillino S (2011) Is ranibizumab effective in stopping the loss of vision for choroidal neovascularisation in pathologic myopia? A long-term follow-up study. Br J Ophthalmol 95: 657-661
24. Hayashi K, Shimada N, Moriyama M, Hayashi W, Tokoro T, Ohno-Matsui K (2011) Two-Year Outcomes of Intravitreal Bevacizumab for Choroidal Neovascularization in Japanese Patients with Pathologic Myopia. Retina DOI: 10.1097/IAE.0b013e3182278bae
25. Ikuno Y, Sayanagi K, Soga K, Sawa M, Tsujikawa M, Gomi F, Tano Y (2009) Intravitreal bevacizumab for choroidal neovascularization attributable to pathological myopia: one-year results. Am J Ophthalmol 147: 94-100
26. Hayashi K, Ohno-Matsui K, Teramukai S, Shimada N, Moriyama M, Hayashi W, Yoshida T, Tokoro T, Mochizuki M (2009) Comparison of visual outcome and regression pattern of myopic choroidal neovascularization after intravitreal bevacizumab or after photodynamic

therapy. Am J Ophthalmol 148: 396-408

27. Baba T, Kubota-Taniai M, Kitahashi M, Okada K, Mitamura Y, Yamamoto S (2010) Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularisation. Br J Ophthalmol 94: 864-870
28. El Matri L, Kort F, Chebil A, Bouraoui R, Merdassi A, Bouladi M (2011) Intravitreal bevacizumab versus photodynamic therapy for myopic choroidal neovascularization in a North-African population. Graefes Arch Clin Exp Ophthalmol DOI: 10.1007/s00417-011-1654-4
29. Ikuno Y, Nagai Y, Matsuda S, Arisawa A, Sho K, Oshita T, Takahashi K, Uchihori Y, Gomi F (2010) Two-year visual results for older Asian women treated with photodynamic therapy or bevacizumab for myopic choroidal neovascularization. Am J Ophthalmol 149: 140-146
30. Voykov B, Gelisken F, Inhoffen W, Voelker M, Bartz-Schmidt KU, Ziemssen F (2010) Bevacizumab for choroidal neovascularization secondary to pathologic myopia: Is there a decline of the treatment efficacy after 2 years? Graefes Arch Clin Exp Ophthalmol 248: 543-550
31. Ruiz-Moreno JM, Montero JA (2010) Intravitreal bevacizumab to treat myopic choroidal neovascularization: 2-year outcome. Graefes Arch Clin Exp Ophthalmol 248: 937-941
32. Franqueira N, Cachulo ML, Pires I, Fonseca P, Marques I, Figueira J, Silva R (2011) Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. Ophthalmologica DOI: 000333213 [pii] 10.1159/000333213
33. Yamashiro K, Tsujikawa A, Miyamoto K, Oh H, Otani A, Tamuara H, Ooto S, Sasahara M, Iwama D, Yoshimura N (2010) Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. Retina 30: 485-490
34. Ruiz-Moreno JM, Amat P, Montero JA, Lugo F (2008) Photodynamic therapy to treat choroidal neovascularisation in highly myopic patients: 4 years' outcome. Br J Ophthalmol 92: 792-794
35. Hayashi K, Ohno-Matsui K, Yoshida T, Kobayashi K, Kojima A, Shimada

N, Yasuzumi K, Futagami S, Tokoro T, Mochizuki M (2005) Characteristics of patients with a favorable natural course of myopic choroidal neovascularization. Graefes Arch Clin Exp Ophthalmol 243: 13-19

36. Kojima A, Ohno-Matsui K, Teramukai S, Yoshida T, Ishihara Y, Kobayashi K, Shimada N, Yasuzumi K, Futagami S, Tokoro T, Mochizuki M (2004) Factors associated with the development of chorioretinal atrophy around choroidal neovascularization in pathologic myopia. Graefes Arch Clin Exp Ophthalmol 242: 114-119
37. Axer-Siegel R, Ehrlich R, Weinberger D, Rosenblatt I, Shani L, Yassur Y, Priel E, Kramer M (2004) Photodynamic therapy of subfoveal choroidal neovascularization in high myopia in a clinical setting: visual outcome in relation to age at treatment. Am J Ophthalmol 138: 602-607
38. Montero JA, Ruiz-Moreno JM (2003) Verteporfin photodynamic therapy in highly myopic subfoveal choroidal neovascularisation. Br J Ophthalmol 87: 173-176
39. Nakanishi H, Tsujikawa A, Yodoi Y, Ojima Y, Otani A, Tamura H, Yamashiro K, Ooto S, Yoshimura N (2011) Prognostic factors for visual outcomes 2-years after intravitreal bevacizumab for myopic choroidal neovascularization. Eye (Lond) 25: 375-381
40. Soubrane G (2008) Choroidal neovascularization in pathologic myopia: recent developments in diagnosis and treatment. Surv Ophthalmol 53: 121-138

Figure legends

Figure 1. Color fundus photographs of a representative case with subfoveal choroidal neovascularization (CNV) (left, pretreatment; triangle, CNV). Patchy atrophy was not evident after 1 year (middle) but developed thereafter (right, 48 months after the treatment; arrow, CRA).

Figure 2. Color fundus photographs and fluorescein angiography image of a 62-year-old woman. She had subfoveal CNV (upper left and middle panels; triangle, CNV) and was administered 2 bevacizumab injections. Chorioretinal atrophy (arrows) developed as early as 1 year after treatment (upper right) and progressed further thereafter (lower left, middle, and right panels: 2, 3, and 4 years, respectively). Her visual acuity, calculated as logMAR, improved from 0.15 to 0.4 in 1 year but declined to 0.2 in the subsequent year, ultimately reaching 0.08.

Figure 3. Color fundus photographs and fluorescein angiography image of a 77-year-old woman. She had juxtafoveal mCNV (upper left and middle panels; triangle) and her left visual acuity, calculated as logMAR, was 0.1. mCNV diminished with an intravitreal injection of bevacizumab, and chorioretinal atrophy was not evident initially (upper right,1 year after treatment). However, CNV recurred in 20 months (lower left; triangle) and after 6 additional injections, chorioretinal atrophy (arrows) developed and enlarged (lower middle and right panels: 3 and 4 years, respectively). Finally, her visual acuity was 0.05.

Figure 4. Color fundus photographs and fluorescein angiography image of a 74-year-old man with juxtafoveal mCNV and visual acuity of 0.3 (upper left and middle panels, triangle). With a single injection of bevacizumab, mCNV efficiently regressed (upper right, 1 year after the treatment). Although the peripapillary atrophy enlarged within this period, mCNV-related chorioretinal atrophy was not noted (lower left, middle, and right panels: 2, 3, and 4 years

after treatment, respectively), and favorable improvement in vision was achieved (final visual acuity was 0.9).

Figure 5. Changes in visual acuity as a function of time. Dot plots represent mean values, and whiskers represent 95% confidence intervals. Visual acuity improvement was roughly maintained during the 4-year period despite the p value being barely non-significant in the fourth year. * $P < .05$ and ** $P < .01$ compared to baseline.

Tables

TABLE 1. Characteristics of patients with and without chorioretinal atrophy progression 4 years after intravitreal injection of bevacizumab.

	CRA	Non-CRA	*P* value
Age (years)	63.5 ± 10.7	65.7 ± 6.3	n.s.
Sex (male/female)	5/11	2/4	n.s.
Axial length (mm)	29.06 ± 1.52	28.32 ± 1.96	n.s.
Baseline logMAR (unit)	0.76 ± 0.38	0.76 ± 0.22	n.s.
Final logMAR (unit)	0.67 ± 0.51	0.38 ± 0.39	n.s.
Visual improvement	0.10 ± 0.34	-0.37 ± 0.33	*P* = .049
Area of CNV (mm^2)	1.55 ± 1.21	1.03 ± 0.79	n.s.
Location of CNV (subfovea/juxtafovea)	10/6*	2/4	n.s.
Number of injections	2.1 ± 1.7	2.2 ± 2.4	n.s.

CRA: chorioretinal atrophy progression; logMAR: logarithm of the minimum angle of resolution; CNV: chorioretinal atrophy

*One eye with juxtafoveal CNV showed recurrence involving the subfovea.

Acknowledgment

Funding/support: none. Financial disclosures: The authors have no proprietary interest in any aspect of this study.

Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization

Akio Oishi, Kenji Yamashiro, Akitaka Tsujikawa, Sotaro Ooto, Hiroshi Tamura, Isao Nakata, Masahiro Miyake, Nagahisa Yoshimura

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Corresponding author:

Akio Oishi, Department of Ophthalmology, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto 606-8507, Japan

Tel: +81-75-751-3250

Fax: +81-75-752-0933

E-mail: aquio@kuhp.kyoto-u.ac.jp

There is no financial support or propriety interest concerning the article.

Abstract

Purpose: To investigate the long-term visual prognosis and progression of chorioretinal atrophy in patients with myopic choroidal neovascularization (mCNV) treated with intravitreal injections of Bevacizumab.

Methods: Hospital-based, retrospective cross sectional study. In total, 22 patients (22 eyes) with treatment-naïve mCNV who underwent intravitreal injection of bevacizumab and were followed up for more than 48 months were investigated. Visual acuity and fundus photographs before and 1, 2, 3, and 4 years after initial treatment in the clinics were compared and judged if chorioretinal atrophy (CRA) developed/enlarged or remained unchanged. The influence of clinical characteristics including age, sex, axial length, baseline visual acuity, CNV area, CNV location, and number of injections were investigated with logistic regression analysis.

Results: Mean logarithm of the minimum angle of resolution (logMAR) improved from 0.76 to 0.52 ($P < .01$), 0.48 ($P < .01$), and 0.54 ($P < .05$) after 1, 2, and 3 years, respectively. The effect slightly declined to marginally non-significant levels after 4 years (logMAR, 0.59; $P = .07$). CRA developed or enlarged in 9 cases (41%) in 1 year, reaching 16 cases (73%) at the final visit. Those without CRA enlargement achieved better visual improvement. None of the aforementioned patient characteristics significantly affected CRA.

Conclusions: Anti-VEGF therapy for mCNV is effective for vision improvement in the long term. On the other hand, development or enlargement of CRA frequently occurred and affected visual improvement. Strategies to manage atrophy should be the next step in achieving better visual outcome upon mCNV treatment.

Introduction

Pathologic myopia is one of the major causes of visual impairment worldwide. The disease, marked by elongation of axial length and changes in the fundus of the eye, may cause complications such as posterior staphyloma, chorioretinal atrophy (CRA), or choroidal neovascularization (CNV). Considering that myopia is more prevalent in younger populations,[1, 2] the impact on social health will be more profound in the near future.

Myopic CNV (mCNV) is reported to occur in up to 10% of myopic patients,[3] with a prevalence of up to 40% in highly myopic patients.[4] Since long-term visual prognosis is poor in the absence of treatment,[5, 6] a wide range of therapeutic alternatives, including photocoagulation, macular translocation, surgical CNV removal, administration of triamcinolone acetonide, and photodynamic therapy (PDT), have been explored.[7] Although PDT can stabilize the disease activity, formation of subretinal fibrosis[8] or CRA, a cause of the poor natural course of mCNV,[6, 9] frequently occurs after the treatment,[10] and may affect visual function significantly in the long term. In fact, the most reliable trial (Verteporfin In Photodynamic Therapy: VIP study) failed to show significant improvement in vision 2 years after the treatment.[11]

After the PDT era, anti-vascular endothelial growth factor (VEGF) therapy was developed and proved to be effective against mCNV.[12-24] Although the treatment regimens were not equivalent in these studies, intravitreal anti-VEGF therapy seems to promote the regression of CNV more effectively and decrease the frequency of CRA, compared to PDT.[25-28] However, even with anti-VEGF therapy, CRA still develops[17, 18, 24, 25] and may affect the long-term visual prognosis. [24] In fact, vision improvement became non-significant in some of these studies by the end of 2 years of follow-up.[17, 29-31] Although a recent report showed favorable effects after 3 years of follow-up,[32] some of the studied subjects had previously been treated with PDT. Thus, long-term prognosis of anti-VEGF therapy, especially for treatment-naïve mCNV, is still unclear.

In the present study, we investigated long-term visual prognosis of treatment-naïve mCNV patients who underwent anti-VEGF therapy. We also investigated how often CRA progression occurs in these patients, and explored the difference between those with and without CRA enlargement.

Methods

All procedures conformed to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board at Kyoto University Graduate School of Medicine. Written informed consent was obtained from each patient.

We retrospectively reviewed the clinical records of mCNV patients. Inclusion criteria were as follows: 1) presence of subfoveal or juxtafoveal CNV, 2) refractive error greater or equal to -6.0 diopters or axial length greater or equal to 26.5 mm, 3) underwent intravitreal injection of 1.25 mg bevacizumab at Kyoto University Hospital, and 4) no previous ocular surgery other than phacoemulsification and aspiration for cataract. When both eyes of one patient met the inclusion criteria, only the right eye was included. Exclusion criteria were: 1) any treatment for mCNV other than anti-VEGF therapy prior to or during the observation period, 2) a follow-up period of less than 48 months, and 3) intraocular surgery or development of other ocular diseases during the follow-up.

Initial and follow-up fluorescein angiography (FA) was performed with a confocal scanning laser ophthalmoscope (HRA2; Heidelberg Engineering, Heidelberg, Germany), and 45-degree fundus photographs are taken with a fundus camera (TRC NW6S; TOPCON, Tokyo, Japan). Injections of 1.25 mg bevacizumab were performed under sterile conditions, and prophylactic topical antibiotics were applied from a few days before to 1 week after the injection. Follow-up intervals were 1, 3, 6, 12, 18, 24, 30, 36, and 48 months. Additional follow-up was planned for each patient at the clinician’s discretion. Visual acuity, funduscopic examination, and optical coherence tomography (OCT) examination were performed at each visit. FA was performed when subjective symptoms worsens but OCT does not show obvious exudative changes. After

the initial treatment, additional treatment was applied as needed. The need for re-treatment was determined according to objective/subjective decline of vision, exudative changes in OCT images, and/or dye leakage in FA. Same dose of Bevacizumab had been injected for re-treatment until December, 2008 when we encountered the outbreak of aseptic endophthalmitis. [33] Thereafter, 0.3 mg of Pegaptanib had been used for five months. Then after use of Ranibizumab was officially approved in May 2009, 0.5 mg of Ranibizumab was applied for the recurrences.

Development or enlargement of CRA was judged with photographs taken each year by 2 of the authors (AO and KY) who were blinded to the other characteristics of the patient. The judgment was based on changes in patchy atrophy; color changes in tessellation or diffuse atrophy without patchy atrophy were not considered as CRA progression (Figure 1). CRAs, which were not adjacent to original CNV location, were not counted. When the 2 authors disagreed, a third author (AT) was asked to arbitrate. The CNV area was manually measured in early-phase FA images with measuring tools, which were coupled to the HRA2. Location of CNV was judged from FA; those involving the center of the foveal avascular area on FA were judged as subfoveal. When it was difficult to judge only from FA images, OCT images were used to confirm whether CNV membranes lied beneath the fovea.

Statistical analyses were conducted using IBM SPSS Statistics Desktop (version 19.0; IBM Japan, Tokyo, Japan). Descriptive analyses were recorded as means ± standard deviation unless otherwise specified. The BCVA was measured based on a Landolt C chart and then converted to logarithm of the minimal angle of resolution (logMAR) equivalents. Differences in VA from baseline were analyzed using repeated measures ANOVA with post-hoc Tukey's test. Logistic regression analysis of the clinical variables was performed with development/enlargement of CRA as the dependent variable. Independent variables were chosen based on forward stepwise regression. Correlations between the variables were also evaluated with Spearman rank correlation. Differences in age, axial length, BCVA, and number of injections between those

with and without CRA progression were evaluated with Mann–Whitney *U*-test. Chi-square test was applied to assess the difference in sex or CNV location (subfovea/juxtafovea) between those with and without CRA progression.

Results

Forty eyes of 40 patients met the inclusion criteria. Two patients had bilateral involvement but only their right eyes were included. We excluded one patient who developed aseptic endophthalmitis, one who developed central retinal vein occlusion, 2 who underwent vitrectomy for retinoschisis, and 4 who underwent additional PDT. Ten patients dropped out before the end of the 48 months of follow-up. Finally, 22 eyes of 22 patients were eligible for the study. Among them, 7 were men and 15 were women. The mean age of the participants was 64.1 ± 9.6 years (range, 47 to 81 years), and axial length was 28.9 ± 1.6 mm (range, 26.28 to 32.63 mm). The refractive error of phakic patients was -11.9 ± 3.7 diopter (range, -7 to -21). Mean number of injections was 2.1 ± 1.9 (range, 1 to 7) including 41 times of Bevacizumab and six times of Ranibizumab injections.

Development or enlargement of CRA was noted in 9 eyes (40.9%) in 1st year, 14 eyes (63.6%) in 2nd years, and 16 eyes (72.7%) in 3rd and 4th years; those without CRA progression after 3 years did not show remarkable change in the fourth year. Logistic regression analysis showed non-significant effect of age (P = .08) and location of CNV for CRA progression at 1 year (P = .07). After 2 years, none of the parameters showed significant effect. Table 1 shows characteristics of those with and without CRA progression at 4 years after the treatment. Visual improvement was better in those without CRA progression than those with CRA progression. Those without CRA progression tended to include juxtafoveal CNV more frequently but the difference was not significant (P = .21). Representative cases are shown in Figures 1–5. Some patients developed CRA early after the treatment (Figure 1), whereas others developed CRA after 1 or 2 years (Figure 2). The minority of patients was free of CRA

progression during the course of the 48-month follow-up (Figure 3).

Visual acuity improved from baseline but slightly declined thereafter. The difference from baseline was significant until 3 years and was marginally insignificant at 4 years after the treatment (Figure 4). Among the baseline CNV characteristics, CNV size measured with FA image was associated with visual improvement (r=.434, P=.04); larger CNV resulted in poor visual improvement.

Discussion

We investigated long-term visual outcome and progression of CRA in treatment-naïve mCNV patients who underwent anti-VEGF therapy. The study showed significant improvement of vision over the 3 years of follow-up, despite that the *P* value was barely non-significant in the fourth year, and confirmed the beneficial effect of anti-VEGF therapy for mCNV. At the same time, the study showed that most patients finally experience the progression of CRA irrespective of baseline characteristics, and that CRA compromises the vision-improving effect.

Anti-VEGF therapy is becoming a standard treatment for mCNV although its application is not yet officially approved in many countries. The present study confirmed the long-term effect of the therapy. Considering that the effect of PDT is limited to maintain vision,[10,][34] anti-VEGF therapy should be the first choice until a novel method is proven to be more effective.

On the other hand, the present study raised some concerns regarding longer-term prognosis: the progression of CRA. Anti-VEGF therapy is considered to be superior to PDT partly because it induces CRA less frequently. However, the present result showed that the assumption is not necessarily applicable in the long term. In fact, CRA developed or enlarged in as many as 80% of the patients. Even considering that only 3/10 dropout patients showed CRA progression at their final visit, the percentage of patients with CRA progression should be at least $[(16 + 3)/(22 + 10)] \times 100 = 59.4\%$. This figure is comparable to the 70% in PDT-treated eyes after 4 years,[10] or the 77.8%

(35/45 eyes) in eyes after the natural course of 5 years[35] but not to the 95.1% reported for the 80 months result.[36] Hence, CRA progression is often an inevitable consequence in the long-term follow-up of mCNV cases, probably due to natural history but to anti-VEGF therapy. Considering that those with CRA progression showed less visual improvement, the control of CRA should be the next step to be investigated.

Older age has been associated with development of CRA[36] or poor visual outcome.[37],[38] However, the present study did not show significant contribution of age for the development of CRA. One explanation could be the existence of a critical age. Most of the previous studies investigated age-dependent differences by comparing aged and younger patients of 40 to 60 years of age. The population in the present study consisted of relatively older subjects; the average and median age of the participants in the present study was 64.1 and 64 years, respectively. A small percentage of young patients could explain the non-significant effect of age.

The location of CNV is of clinical interest. Several groups, including ours, showed that patients with juxtafoveal CNV have better prognosis than subfoveal CNV during the natural course of the disease[35] or after anti-VEGF therapy.[18, 39] Moreover, subfoveal CNV induces larger CRA after PDT than do juxtafoveal or extrafoveal CNV[10] or induce CRA more frequently after intravitreal injection of Bevacizumab.[24] In the present study, subfoveal CNV tended to cause CRA progression more frequently at 1 year after the initial treatment, although this was not statistically significant. Furthermore, 4 out of 6 patients who were free of CRA for 4 years had juxtafoveal CNV. The statistical non-significance may be partly due to the small sample size and the difficulty in treating recurrent cases: one case with juxtafoveal CNV recurred with subfoveal CNV and developed CRA thereafter. Although the underlying mechanism is not clear, e.g., could subfoveal CNV be a mere result of larger CNV size?, whether the location of CNV can be a practical prognostic parameter of CRA progression should be further investigated.

There still is a debate about which protocol is the most effective. Some

authors used 3 monthly injections at the loading phase, whereas others adopted a single injection followed by additional as-needed injections. The dose of the drug also varies among reports, with 1, 1.25, and 2.5 mg of bevacizumab having been reported to be effective. Although we cannot draw any conclusion from the non-comparative study, we prefer the single injection and as-needed regimen due to lower risk and smaller cost, considering the relatively young age, healthier RPE, and slower progression of mCNV[40] compared to age-related macular degeneration. Randomized or meta-analysis study should be conducted to address the issue.

There are several limitations to the present study, including its retrospective design, uncontrolled examination interval, small sample size, and lack of a control group. In addition, there have existed a selection bias, e.g., patients with persistent or recurrent CNV would more likely present to the hospital for a longer period or, conversely, patients with severe phenotypes might have undergone additional PDT and be excluded from the study. In addition, we did not investigate OCT images in detail because the resolution of the devices used when the patients underwent initial treatment was limited. Further evaluation of pretreatment OCT image including retinal layer thickness or choroidal thickness would be interesting. These points should be noted when interpreting the results.

In conclusion, we showed that anti-VEGF therapy had satisfactory vision-improving effect for a 4-year period but the treatment was not free of inducing CRA. To achieve better results, the causes and management of CRA should be further investigated.

References

1. Mutti DO, Zadnik K (2000) Age-related decreases in the prevalence of myopia: longitudinal change or cohort effect? Invest Ophthalmol Vis Sci 41: 2103-2107
2. Lee KE, Klein BE, Klein R, Wong TY (2002) Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. Invest Ophthalmol Vis Sci 43: 2566-2571
3. Curtin BJ (1963) The pathogenesis of congenital myopia. A study of 66 cases. Arch Ophthalmol 6: 166-173
4. Hotchkiss ML, Fine SL (1981) Pathologic myopia and choroidal neovascularization. Am J Ophthalmol 91: 177-183
5. Tabandeh H, Flynn HWJ, Scott IU, Lewis ML, Rosenfeld PJ, Rodriguez F, Rodriguez A, Singerman LJ, Schiffman J (1999) Visual acuity outcomes of patients 50 years of age and older with high myopia and untreated choroidal neovascularization. Ophthalmology 106: 2063-2067
6. Yoshida T, Ohno-Matsui K, Yasuzumi K, Kojima A, Shimada N, Futagami S, Tokoro T, Mochizuki M (2003) Myopic choroidal neovascularization: a 10-year follow-up. Ophthalmology 110: 1297-1305
7. Chan WM, Ohji M, Lai TY, Liu DT, Tano Y, Lam DS (2005) Choroidal neovascularisation in pathological myopia: an update in management. Br J Ophthalmol 89: 1522-1528
8. Ruiz-Moreno JM, Montero JA (2003) Subretinal fibrosis after photodynamic therapy in subfoveal choroidal neovascularisation in highly myopic eyes. Br J Ophthalmol 87: 856-859
9. Ohno-Matsui K, Yoshida T (2004) Myopic choroidal neovascularization: natural course and treatment. Curr Opin Ophthalmol 15: 197-202
10. Hayashi K, Ohno-Matsui K, Shimada N, Moriyama M, Hayashi W, Wang J, Yoshida T, Tokoro T, Mochizuki M (2011) Long-term results of photodynamic therapy for choroidal neovascularization in Japanese patients with pathologic myopia. Am J Ophthalmol 151: 137-147
11. Blinder KJ, Blumenkranz MS, Bressler NM, Bressler SB, Donato G, Lewis

H, Lim JI, Menchini U, Miller JW, Mones JM, Potter MJ, Pournaras C, Reaves A, Rosenfeld P, Schachat AP, Schmidt-Erfurth U, Sickenberg M, Singerman LJ, Slakter JS, Strong HA, Virgili G, Williams GA (2003) Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial--VIP report no. 3. Ophthalmology 110: 667-673

12. Gharbiya M, Allievi F, Mazzeo L, Gabrieli CB (2009) Intravitreal bevacizumab treatment for choroidal neovascularization in pathologic myopia: 12-month results. Am J Ophthalmol 147: 84-93
13. Konstantinidis L, Mantel I, Zografos L, Ambresin A (2009) Intravitreal ranibizumab as primary treatment for neovascular membrane associated with idiopathic juxtafoveal retinal telangiectasia. Graefes Arch Clin Exp Ophthalmol 247: 1567-1569
14. Silva RM, Ruiz-Moreno JM, Rosa P, Carneiro A, Nascimento J, Rito LF, Cachulo ML, Carvalheira F, Murta JN (2010) Intravitreal Ranibizumab for Myopic Choroidal Neovascularization 12-Month Results. Retina 30: 407-412
15. Mones JM, Amselem L, Serrano A, Garcia M, Hijano M (2009) Intravitreal ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results. Eye (Lond) 23: 1275-1280
16. Lai TY, Chan WM, Liu DT, Lam DS (2009) Intravitreal ranibizumab for the primary treatment of choroidal neovascularization secondary to pathologic myopia. Retina 29: 750-756
17. Lalloum F, Souied EH, Bastuji-Garin S, Puche N, Querques G, Glacet-Bernard A, Coscas G, Soubrane G, Leveziel N (2010) Intravitreal ranibizumab for choroidal neovascularization complicating pathologic myopia. Retina 30: 399-406
18. Calvo-Gonzalez C, Reche-Frutos J, Donate J, Fernandez-Perez C, Garcia-Feijoo J (2011) Intravitreal ranibizumab for myopic choroidal neovascularization: factors predictive of visual outcome and need for retreatment. Am J Ophthalmol 151: 529-534
19. Falcao-Reis FM, Carneiro AM, Silva RM, Veludo MJ, Barbosa A,

Ruiz-Moreno JM, Falcao MS, Brandao EM (2011) Ranibizumab treatment for choroidal neovascularization from causes other than age-related macular degeneration and pathological myopia. Ophthalmologica 225: 81-88

20. Iacono P, Parodi MB, Papayannis A, Kontadakis S, Sheth S, Bandello F (2011) Intravitreal bevacizumab therapy on an as-per-needed basis in subfoveal choroidal neovascularization secondary to pathological myopia: 2-year outcomes of a prospective case series. Retina 31: 1841-1847
21. Ruiz-Moreno JM, Montero JA, Arias L, Araiz J, Gomez-Ulla F, Silva R, Pinero DP (2010) Twelve-month outcome after one intravitreal injection of bevacizumab to treat myopic choroidal neovascularization. Retina 30: 1609-1615
22. Chen CH, Wu PC, Chen YJ, Liu YC, Kuo HK (2011) Intravitreal injection of 2.5 mg bevacizumab for treatment of myopic choroidal neovascularization in treatment-naive cases: a 2-year follow-up. J Ocul Pharmacol Ther 27: 395-400
23. Vadala M, Pece A, Cipolla S, Monteleone C, Fasolino G, Casuccio A, Cillino S (2011) Is ranibizumab effective in stopping the loss of vision for choroidal neovascularisation in pathologic myopia? A long-term follow-up study. Br J Ophthalmol 95: 657-661
24. Hayashi K, Shimada N, Moriyama M, Hayashi W, Tokoro T, Ohno-Matsui K (2011) Two-Year Outcomes of Intravitreal Bevacizumab for Choroidal Neovascularization in Japanese Patients with Pathologic Myopia. Retina DOI: 10.1097/IAE.0b013e3182278bae
25. Ikuno Y, Sayanagi K, Soga K, Sawa M, Tsujikawa M, Gomi F, Tano Y (2009) Intravitreal bevacizumab for choroidal neovascularization attributable to pathological myopia: one-year results. Am J Ophthalmol 147: 94-100
26. Hayashi K, Ohno-Matsui K, Teramukai S, Shimada N, Moriyama M, Hayashi W, Yoshida T, Tokoro T, Mochizuki M (2009) Comparison of visual outcome and regression pattern of myopic choroidal neovascularization after intravitreal bevacizumab or after photodynamic

therapy. Am J Ophthalmol 148: 396-408

27. Baba T, Kubota-Taniai M, Kitahashi M, Okada K, Mitamura Y, Yamamoto S (2010) Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularisation. Br J Ophthalmol 94: 864-870

28. El Matri L, Kort F, Chebil A, Bouraoui R, Merdassi A, Bouladi M (2011) Intravitreal bevacizumab versus photodynamic therapy for myopic choroidal neovascularization in a North-African population. Graefes Arch Clin Exp Ophthalmol DOI: 10.1007/s00417-011-1654-4

29. Ikuno Y, Nagai Y, Matsuda S, Arisawa A, Sho K, Oshita T, Takahashi K, Uchihori Y, Gomi F (2010) Two-year visual results for older Asian women treated with photodynamic therapy or bevacizumab for myopic choroidal neovascularization. Am J Ophthalmol 149: 140-146

30. Voykov B, Gelisken F, Inhoffen W, Voelker M, Bartz-Schmidt KU, Ziemssen F (2010) Bevacizumab for choroidal neovascularization secondary to pathologic myopia: Is there a decline of the treatment efficacy after 2 years? Graefes Arch Clin Exp Ophthalmol 248: 543-550

31. Ruiz-Moreno JM, Montero JA (2010) Intravitreal bevacizumab to treat myopic choroidal neovascularization: 2-year outcome. Graefes Arch Clin Exp Ophthalmol 248: 937-941

32. Franqueira N, Cachulo ML, Pires I, Fonseca P, Marques I, Figueira J, Silva R (2011) Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. Ophthalmologica DOI: 000333213 [pii] 10.1159/000333213

33. Yamashiro K, Tsujikawa A, Miyamoto K, Oh H, Otani A, Tamuara H, Ooto S, Sasahara M, Iwama D, Yoshimura N (2010) Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. Retina 30: 485-490

34. Ruiz-Moreno JM, Amat P, Montero JA, Lugo F (2008) Photodynamic therapy to treat choroidal neovascularisation in highly myopic patients: 4 years' outcome. Br J Ophthalmol 92: 792-794

35. Hayashi K, Ohno-Matsui K, Yoshida T, Kobayashi K, Kojima A, Shimada

N, Yasuzumi K, Futagami S, Tokoro T, Mochizuki M (2005) Characteristics of patients with a favorable natural course of myopic choroidal neovascularization. Graefes Arch Clin Exp Ophthalmol 243: 13-19

36. Kojima A, Ohno-Matsui K, Teramukai S, Yoshida T, Ishihara Y, Kobayashi K, Shimada N, Yasuzumi K, Futagami S, Tokoro T, Mochizuki M (2004) Factors associated with the development of chorioretinal atrophy around choroidal neovascularization in pathologic myopia. Graefes Arch Clin Exp Ophthalmol 242: 114-119
37. Axer-Siegel R, Ehrlich R, Weinberger D, Rosenblatt I, Shani L, Yassur Y, Priel E, Kramer M (2004) Photodynamic therapy of subfoveal choroidal neovascularization in high myopia in a clinical setting: visual outcome in relation to age at treatment. Am J Ophthalmol 138: 602-607
38. Montero JA, Ruiz-Moreno JM (2003) Verteporfin photodynamic therapy in highly myopic subfoveal choroidal neovascularisation. Br J Ophthalmol 87: 173-176
39. Nakanishi H, Tsujikawa A, Yodoi Y, Ojima Y, Otani A, Tamura H, Yamashiro K, Ooto S, Yoshimura N (2011) Prognostic factors for visual outcomes 2-years after intravitreal bevacizumab for myopic choroidal neovascularization. Eye (Lond) 25: 375-381
40. Soubrane G (2008) Choroidal neovascularization in pathologic myopia: recent developments in diagnosis and treatment. Surv Ophthalmol 53: 121-138

Figure legends

Figure 1. Color fundus photographs of a representative case with subfoveal choroidal neovascularization (CNV) (left, pretreatment; triangle, CNV). Patchy atrophy was not evident after 1 year (middle) but developed thereafter (right, 48 months after the treatment; arrow, CRA).

Figure 2. Color fundus photographs and fluorescein angiography image of a 62-year-old woman. She had subfoveal CNV (upper left and middle panels; triangle, CNV) and was administered 2 bevacizumab injections. Chorioretinal atrophy (arrows) developed as early as 1 year after treatment (upper right) and progressed further thereafter (lower left, middle, and right panels: 2, 3, and 4 years, respectively). Her visual acuity, calculated as logMAR, improved from 0.15 to 0.4 in 1 year but declined to 0.2 in the subsequent year, ultimately reaching 0.08.

Figure 3. Color fundus photographs and fluorescein angiography image of a 77-year-old woman. She had juxtafoveal mCNV (upper left and middle panels; triangle) and her left visual acuity, calculated as logMAR, was 0.1. mCNV diminished with an intravitreal injection of bevacizumab, and chorioretinal atrophy was not evident initially (upper right,1 year after treatment). However, CNV recurred in 20 months (lower left; triangle) and after 6 additional injections, chorioretinal atrophy (arrows) developed and enlarged (lower middle and right panels: 3 and 4 years, respectively). Finally, her visual acuity was 0.05.

Figure 4. Color fundus photographs and fluorescein angiography image of a 74-year-old man with juxtafoveal mCNV and visual acuity of 0.3 (upper left and middle panels, triangle). With a single injection of bevacizumab, mCNV efficiently regressed (upper right, 1 year after the treatment). Although the peripapillary atrophy enlarged within this period, mCNV-related chorioretinal atrophy was not noted (lower left, middle, and right panels: 2, 3, and 4 years

after treatment, respectively), and favorable improvement in vision was achieved (final visual acuity was 0.9).

Figure 5. Changes in visual acuity as a function of time. Dot plots represent mean values, and whiskers represent 95% confidence intervals. Visual acuity improvement was roughly maintained during the 4-year period despite the p value being barely non-significant in the fourth year. * $P < .05$ and ** $P < .01$ compared to baseline.

Tables

TABLE 1. Characteristics of patients with and without chorioretinal atrophy progression 4 years after intravitreal injection of bevacizumab.

	CRA	Non-CRA	*P* value
Age (years)	63.5 ± 10.7	65.7 ± 6.3	n.s.
Sex (male/female)	5/11	2/4	n.s.
Axial length (mm)	29.06 ± 1.52	28.32 ± 1.96	n.s.
Baseline logMAR (unit)	0.76 ± 0.38	0.76 ± 0.22	n.s.
Final logMAR (unit)	0.67 ± 0.51	0.38 ± 0.39	n.s.
Visual improvement	0.10 ± 0.34	-0.37 ± 0.33	*P* = .049
Area of CNV (mm^2)	1.55 ± 1.21	1.03 ± 0.79	n.s.
Location of CNV (subfovea/juxtafovea)	10/6*	2/4	n.s.
Number of injections	2.1 ± 1.7	2.2 ± 2.4	n.s.

CRA: chorioretinal atrophy progression; logMAR: logarithm of the minimum angle of resolution; CNV: chorioretinal atrophy

*One eye with juxtafoveal CNV showed recurrence involving the subfovea.

Acknowledgment

Funding/support: none. Financial disclosures: The authors have no proprietary interest in any aspect of this study.

Figure 1
Click here to download high resolution image

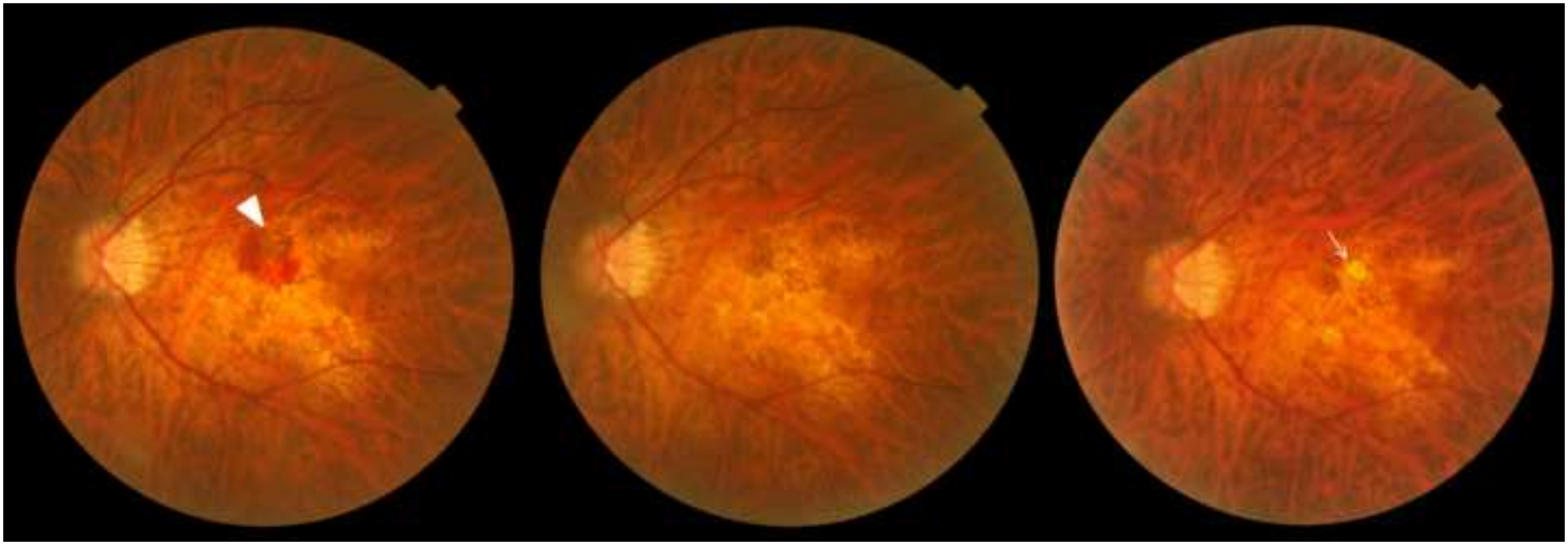


Figure 2
Click here to download high resolution image

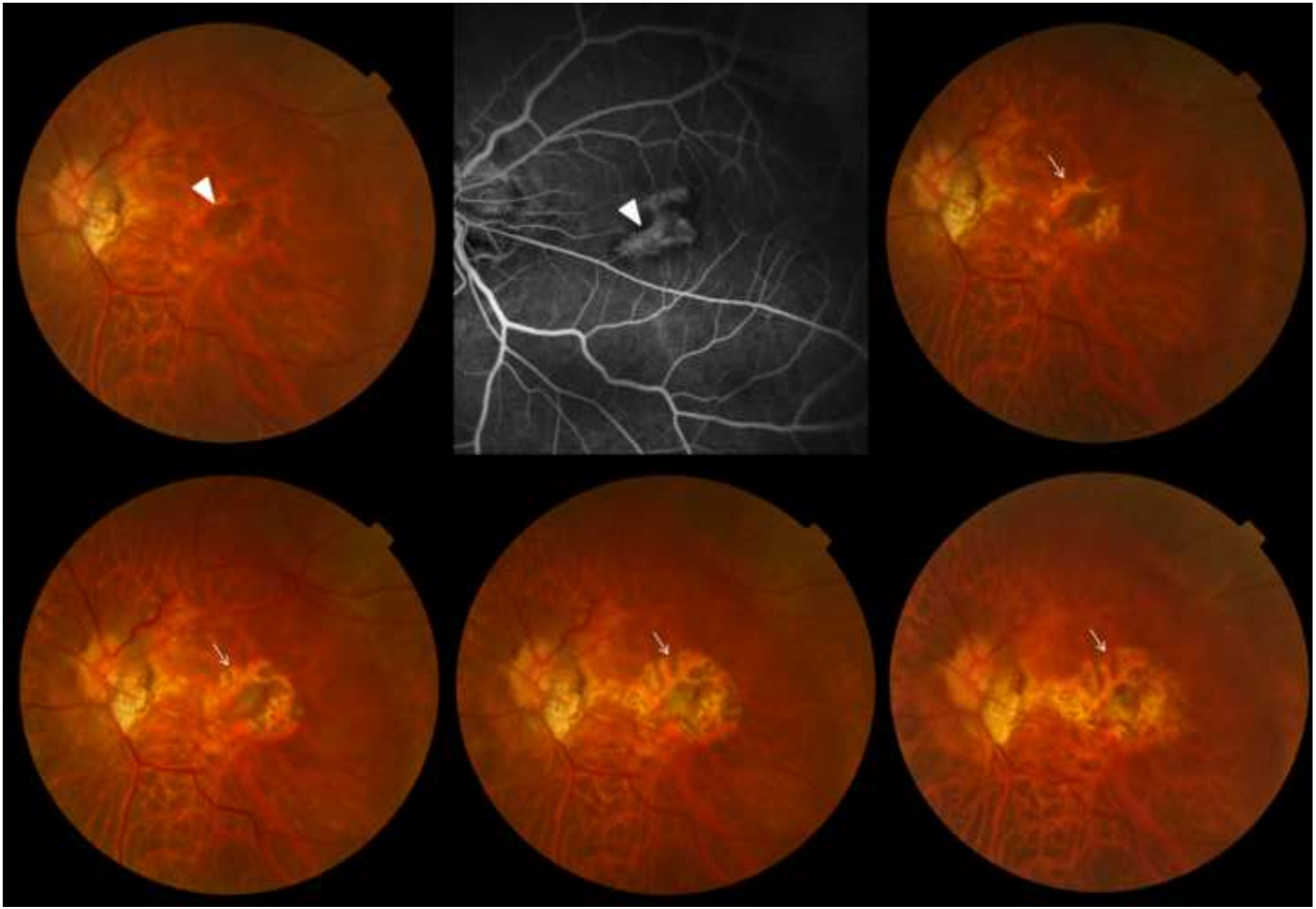


Figure 3
Click here to download high resolution image

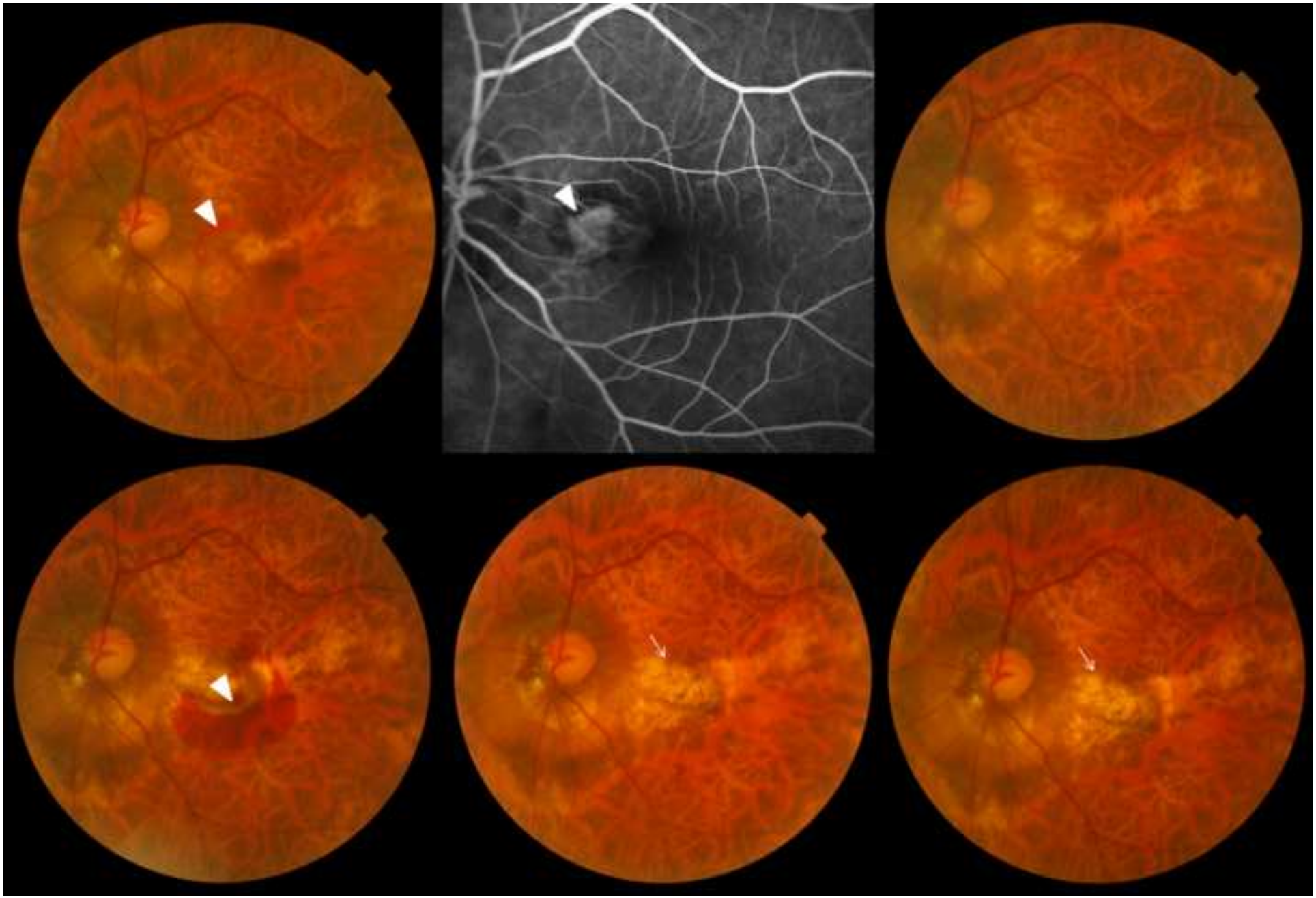


Figure 4
Click here to download high resolution image

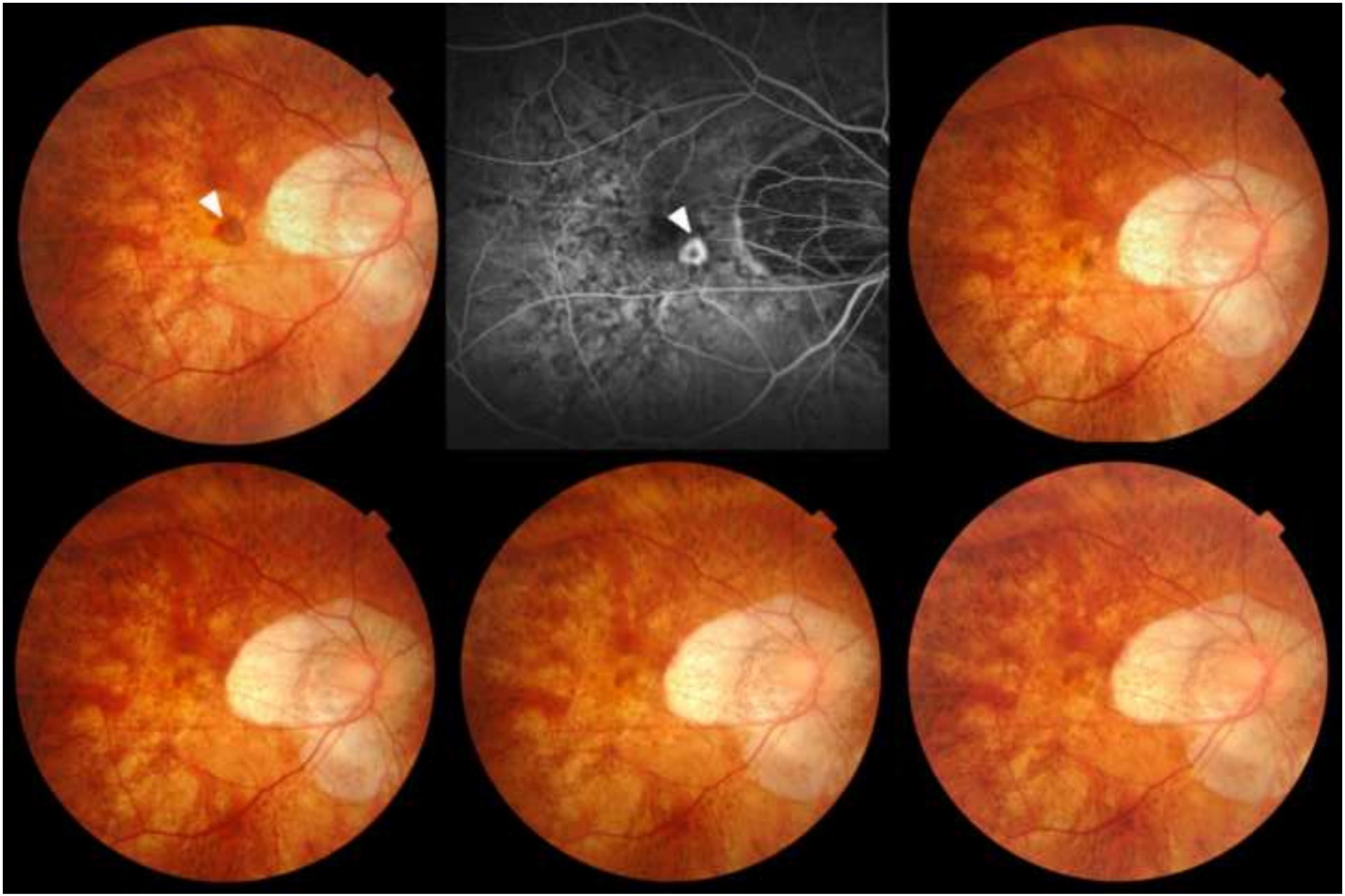
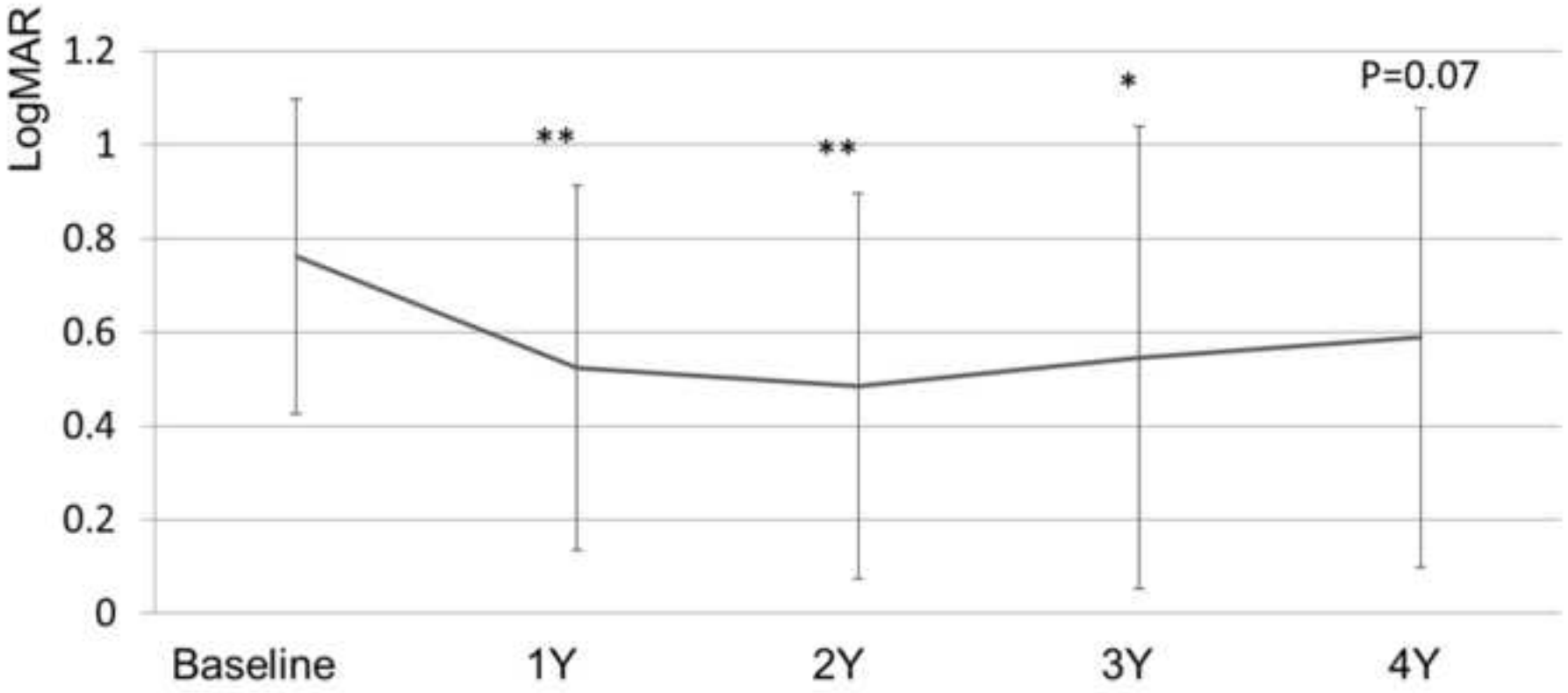


Figure 5
Click here to download high resolution image



Authorship Form: Graefes Archive for Clinical and Experimental Ophthalmology

Title:- Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and choroidal atrophy progression in myopic choroidal neovascularization

I, Akira Oishi hereby confirm that all named authors meet the ICMJE

(corresponding author)

requirement of authorship and meet all three criteria as mentioned below:

1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) drafting the article or revising it critically for important intellectual content; and
3) final approval of the version to be published.
Authors should meet conditions 1, 2, and 3.

*signed:	Akira Oishi	date: 21. Jan. 2012
signed:	Keiji Yamashiri	date: 23. Jan. 2012
signed:	Akihito Uji	date: 23 Jan 2012
signed:	Sotaro Ooto	date: 21 Jan. 2012
signed:	Hiroshi Tamura	date: 23 Jan. 2012
signed:	Akio Oishi	date: 23 Jan. 2012
signed:	Masahiro Miyake	date: 23 Jan 2012
signed:	Nagahisa Yoshimura	date: 23. Jan. 2012
signed:		date:

*First signature should be of corresponding author

The acknowledgment section includes contributors who provided purely technical help, writing assistance, or a department chair who provided only general support. Medical Writers; Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as 'clinical investigators' or 'participating investigators,' and their function or contribution should be described-for example, 'served as scientific advisors,' 'critically reviewed the study proposal,' 'collected data,' or 'provided and cared for study patients.'

I confirm that this paper is not being submitted simultaneously elsewhere.

signed: Akira Oishi date: 21. Jan. 2012

(corresponding author)